Pharmacogenetics Implementation at Cincinnati Children’s Hospital Medical Center (CCHMC)

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Disclosures

- I have nothing to disclose.
Definitions

• Pharmacogenomics: how all of the genes (the genome) can influence responses to drugs

• Pharmacogenetics: how variation in one single gene influences the response to a single drug
Objectives of pharmacogenetics

- Identify variation in response
- Elucidate molecular mechanisms
- Evaluate clinical significance
- Develop screening tests
- Individualize drug therapy
Pharmacogenetic Resources

- PharmGKB
- Pharmacogenetic Research Network (PGRN)
- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - Goal: provide peer-reviewed, updated, evidence-based freely accessible guidelines for gene/drug pairs
  - Guidelines will facilitate translation of pharmacogenomic knowledge from bench to bedside
  - What to do with the genotypes, not whether to genotype
- IGNITE SPARK Toolbox
History of Pharmacogenetics

- 1959 Friedrich Vogel first used term “pharmacogenetics”
- Family studies done between 1960s – 1980s documented patterns of inheritance for many drug effects (therapeutic & adverse)
- 1987: CYP2D6 became first polymorphic human drug-metabolizing gene to be characterized
- 1990s: clinical utility of several genes demonstrated, including TPMT
# Current status of PGx

## Table 1 | Actionable germline genetic variation and associated medications

<table>
<thead>
<tr>
<th>Genetic variation</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>Mercaptopurine, thioguanine, azathioprine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine, tramadol, tricyclic antidepressants</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tricyclic antidepressants, clopidogrel, voriconazole</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin, phenytoin</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Allopurinol, carbamazepine, abacavir, phenytoin</td>
</tr>
<tr>
<td>CFTR</td>
<td>Ivacaftor</td>
</tr>
<tr>
<td>DPYD</td>
<td>Fluorouracil, capecitabine, tegafur</td>
</tr>
<tr>
<td>G6PD</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan, atazanavir</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>IFNL3 (IL28B)</td>
<td>Interferon</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
</tr>
</tbody>
</table>

From ref. 44 (accessed on 7 May 2015). See ref. 44 for updates.
Pharmacogenetic nomenclature

Variant(s) → * alleles → diplotypes → metabolizer status → medication change

- * alleles (CYP2D6*4)
- *1 is usually “wild-type” in Caucasians
- Can contain one or more than one variant
- Some genes have nomenclature committees (PharmVar)
- Sometimes two groups publish new * alleles at the same time with different definitions
- Increase in sequencing and effect of individual variants may change the way this is done
1. Clinical trials provide evidence of efficacy and safety at **usual doses** in **populations**

2. Physicians treat **individual** patients who can vary widely in their response to drug therapy

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**Continuing Paradox of Drug Development**

- **Efficacious & Safe**
- **No Response**
- **Adverse Drug Reaction**

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**Graphs:**
- **Amount of Drug** over **Time (days)**
- **MTX conc [uM]** over **Hours since start of infusion**

**Legend:**
- **Fast clearance**
- **Slow clearance**
GWAS hit for methotrexate clearance: SLCO1B1

Observed distribution (log₁₀ of p value)
SLCO1B1 haplotypes

Ramsey et al. Genome Research 2012
SLCO1B1 diplotypes influence methotrexate clearance

![Box plot showing adjusted methotrexate clearance with SLCO1B1 diplotypes]

- Lower clearance
- Higher clearance
In vitro transport is reduced in haplotypes associated with low MTX clearance.

[Graph showing normalized MTX transport for different SLCO1B1 haplotypes, with *1b haplotype having significantly higher transport compared to others, and 6 pts indicated as singleton.]
SLCO1B1 is the only genome-wide association with MTXCL

A

1279 COG patients
2 dosing regimens

B

1279 COG patients + 699 St. Jude patients
5 dosing regimens
Summary of research on methotrexate clearance

- Both rare & common SNPs in SLCO1B1 contribute to methotrexate clearance variation in ALL patients
- SNPs related to reduced methotrexate clearance in patients had reduced function *in vitro*
- GWAS hit was replicated in an independent group of patients, treated with different doses of methotrexate
Simvastatin dosing based on *SLCO1B1* genotype

- The same common variant that is associated with reduced methotrexate clearance is associated with increased simvastatin AUC and simvastatin-induced myopathy.

- CPIC recommends carriers of rs4149056 (T521C) prescribe a lower dose of simvastatin or an alternative statin (e.g. pravastatin, rosuvastatin) and consider routine CK surveillance.
Collagen–induced arthritis, similar to rheumatoid arthritis & juvenile idiopathic arthritis.

Osteosarcoma, acute lymphoblastic leukemia, arthritis, Crohn’s disease…

Hypothesis

Lower clearance
Higher exposure
Better response?

Slco1b2 genotype influences MTX PK & response

AUC of Methotrexate by Slco1b2 Genotype

Exposure to MTX by Slco1b2 genotype

Response to MTX by Slco1b2 genotype

2 mg/kg subcutaneous MTX in all mice, dosed in afternoon
Folate-deficient diet in all mice
Genotype-guided dosing produces equivalent exposure & response

WT: 2 mg/kg
HET: 1 mg/kg
KO: 0.7 mg/kg
Predicting Response of Methotrexate Treatment

PROMOT

• Multi-site clinical trial enrolling JIA patients who will start methotrexate monotherapy (PIs: Sue Thompson & Mara Becker @ CMH in Kansas City)
• GWAS for methotrexate response at 6 months
• Red blood cell folate polyglutamation at baseline and methotrexate polyglutamation at 6 months (more GWAS)
• Generate algorithm to predict response to methotrexate
• First patient enrolled!
SLCO1B1 is still my favorite gene but...
Healthy until 18 month old then developed language regression autism
- Steroids  Good response
- Anticonvulsants  Fair response
- Antidepressants (SSRIs)  Significant side effects
  - mood lability, sensitive to dose changes, tired
Weekly meetings for 9 months

How do genetic variants contribute to variability in response to medications?

How should dosing be changed?

How should we test?

How should we report?

How should we educate?

How much should we charge?

How should we get reimbursed?

How is it working for the doctors?

How is it working for the patients?
Why Psychiatry?

• The Division of Child and Adolescent Psychiatry was interested in using pharmacogenetics to improve patient care.

• Many of the drugs used in psychiatry are metabolized by common polymorphic enzymes.

• We have the largest pediatric psychiatry inpatient unit in the country:
  − 120 inpatient beds across two campuses as well as outpatient clinics
  − >46,000 outpatient and >29,000 inpatient encounters per year

• The Division of Child and Adolescent Psychiatry chose to make the Psychiatry Panel a part of routine care for their inpatients.
Antidepressant use is common in kids

Neuropsychiatric Medications

- **Antipsychotics**
  - Typical/First generation
  - Atypical/Second generation
  - All block dopamine D2 receptors

- **Antidepressants**
  - Tricyclic Antidepressants (TCAs)
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - Others we won’t talk about today

- **Antiepileptics**

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**Figure 2.** Relative contribution of individual DMEs in the metabolism of psychopharmacological drugs estimated from involvement in the main metabolic pathways (based on data from Hienske et al[6]). As can be seen in the figure, the most important liver enzymes involved in antidepressant and antipsychotic drug metabolism are the CYP450 enzymes CYP2D6, CYP3A4, CYP2C19 and CYP1A2, and to a lesser extent CYP2C9 and CYP286 or DMEs other than CYP450 enzymes.

Molecular Psychiatry, Mar 2013, Vol. 18 Issue 3, p273-287
Variability in response to these drugs can be attributed to many things

Figure courtesy Jeffrey Strawn, MD
Influence of genetics on pharmacokinetics

Substantial variability in each gene’s influence among the medications.
Metabolism of SSRIs

Paroxetine $\xrightarrow{\text{CYP2D6}}$ Paroxetine catechol
$\xrightarrow{\text{CYP3A4}}$ $\xrightarrow{\text{CYP1A2}}$

Fluvoxamine $\xrightarrow{\text{CYP2D6}}$ Fluvoxamine acid
$\xrightarrow{\text{CYP1A2}}$

Fluoxetine $\xrightarrow{\text{CYP2D6}}$ S-norfluoxetine
$\xrightarrow{\text{CYP3A4}}$ $\xrightarrow{\text{CYP2C19}}$ R-norfluoxetine
$\xrightarrow{\text{CYP3A4}}$

Sertraline $\xrightarrow{\text{CYP2C19}}$ N-desmethylsertraline
$\xrightarrow{\text{CYP2D6}}$

Citalopram/ Escitalopram $\xrightarrow{\text{CYP2C19}}$ N-desmethylcitalopram
$\xrightarrow{\text{CYP3A4}}$ $\xrightarrow{\text{CYP2D6}}$ N-didesmethylcitalopram
$\xrightarrow{\text{CYP2D6}}$ N-didesmethylcitalopram

SUPPLEMENTAL FIGURE S1. METABOLISM OF SSRIs, WHERE BOLDED ENZYMES REPRESENT A MAJOR METABOLIC PATHWAY.

★ Active  ★ Less active metabolite

What guidelines are there?

- **CPIC**
  - SSRIs: citalopram, escitalopram, fluvoxamine, paroxetine, sertraline
  - TCAs: amitriptyline & nortriptyline (may be applicable to others also)

- **DPWG**
  - SSRIs: citalopram, escitalopram, sertraline
  - TCAs: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline
  - Antipsychotics: aripiprazole & haloperidol

- **FDA labeling**
  - SSRIs: citalopram, escitalopram, fluvoxamine
  - TCAs: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine
  - Other antidepressants: atomoxetine, vortioxetine
  - Antipsychotics: aripiprazole, perphenazine, thioridazine, clozapine, iloperidone

- “The French National Network of Pharmacogenetics (Réseaunational de pharmacogénétique [RNPGx]) recommends CYP2D6 and CYP2C19 genotyping before initiating an antidepressant treatment, especially in patients with a high risk of toxicity”\(^3^\)
Cincinnati Children’s Hospital Medical Center

- Only children’s hospital in the Cincinnati metropolitan area (population 2.3 million)
- 629-bed non-profit organization
- Operations totaling $2.1 billion annually, ~15,000 employees, 6 million square feet of facilities, including eleven off-site neighborhood facilities
- In 2016, CCHMC had 1.3 million patient encounters, including 92,528 Emergency Department visits, 33,903 surgical procedures and 85,161 outpatient primary care visits
- Focused on providing care for the population in our tristate, patients have come from 61 countries and all 50 states
- Revenues in fiscal year 2016 totaled $2.31 billion, including more than $207 million in research grants (2nd among pediatric institutions for NIH funding)
How we implement PGx now

• Psychiatry Panel, Opioid Panel, single genes (CYP2D6, CYP2C9, CYP2C19, TPMT, VKORC1)
• Performed onsite in CAP/CLIA certified Molecular Genetics Lab
• Reported to Results Report tab in Epic
• Report (pdf) contains genotype, phenotype & dosing recommendations as percentage of normal dose (not drug selection)
• When a provider enters an order for a medication with clinical decision support, they see alert
Failure of “one size fits all” approach

- 279 inpatients age 3-18 who received psychotropic medications metabolized by these enzymes

Genotype-guided dosing would have helped these patients achieve better response and less toxicity
>24,000 GPS tests performed over 13 years

- Yearly averages:
  - Psych panel: ~1900
  - Opioid panel: 50–200
  - TPMT: ~120
  - CYP2C19: ~120
  - Warfarin: 10-20
Fluoxetine ordered

RESULTS:

Gene Analyzed

- CYP2C19
- CYP2D6

CLINICAL RECOMMENDATIONS

The use of pharmacogenetic data can help guide the use of drugs. The 19 medications listed have documented pharmacogenetic variability. Based on your standard dose, here are the considerations:

- **50%-100%**: No significant changes needed.
- **75%-100%**: Slight decrease under standard dose. Standard titration indicated.
- **>125%**: Slight increase; standard dose may be indicated.
- **>150%**: Increase over standard dose; faster titration may be indicated.

ADDITIONAL CONSIDERATIONS

Concomitant medication, concurrent diseases, botanical (herbal) medicines, and foods may alter the metabolism or clinical effect of the above medications. We recommend you consult a pharmacist with specific therapy-related questions.

A more complete description of the genetic and non-genetic factors affecting dose-serum concentration-response relationships for a specific drug can be found at [www.cincinnatichildrens.org/gps](http://www.cincinnatichildrens.org/gps).

After consideration of both the genetic and non-genetic factors, if there is a significant deviation from the expected serum concentration, please consider discussing this with a Genetic Pharmacology consultation by sending an email to [GPSConsult@cchmc.org](mailto:GPSConsult@cchmc.org).

METHODOLOGY
Only 36% of patients are normal for both genes

### CYP2D6

<table>
<thead>
<tr>
<th>Metabolizer</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4255</td>
<td>84.6%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>351</td>
<td>7.0%</td>
</tr>
<tr>
<td>Poor</td>
<td>308</td>
<td>6.1%</td>
</tr>
<tr>
<td>Ultra-rapid</td>
<td>116</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

- **CYP2C19**
  - Normal: 2147 (42.7%)
  - Intermediate: 1075 (21.4%)
  - Poor: 151 (3.0%)
  - Ultra-rapid: 1657 (32.9%)

### CYP2C19 metabolizer

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>%</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM</td>
<td>NM</td>
<td>35.8%</td>
<td>1803</td>
</tr>
<tr>
<td>NM</td>
<td>IM</td>
<td>18.4%</td>
<td>925</td>
</tr>
<tr>
<td>NM</td>
<td>PM</td>
<td>2.4%</td>
<td>121</td>
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<tr>
<td>NM</td>
<td>UM</td>
<td>28.0%</td>
<td>1406</td>
</tr>
<tr>
<td>IM</td>
<td>NM</td>
<td>3.0%</td>
<td>151</td>
</tr>
<tr>
<td>IM</td>
<td>IM</td>
<td>1.5%</td>
<td>75</td>
</tr>
<tr>
<td>IM</td>
<td>PM</td>
<td>0.4%</td>
<td>19</td>
</tr>
<tr>
<td>IM</td>
<td>UM</td>
<td>2.1%</td>
<td>106</td>
</tr>
<tr>
<td>PM</td>
<td>NM</td>
<td>2.8%</td>
<td>140</td>
</tr>
<tr>
<td>PM</td>
<td>IM</td>
<td>1.1%</td>
<td>55</td>
</tr>
<tr>
<td>PM</td>
<td>PM</td>
<td>0.2%</td>
<td>8</td>
</tr>
<tr>
<td>PM</td>
<td>UM</td>
<td>2.1%</td>
<td>105</td>
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<tr>
<td>UM</td>
<td>NM</td>
<td>1.1%</td>
<td>53</td>
</tr>
<tr>
<td>UM</td>
<td>IM</td>
<td>0.4%</td>
<td>20</td>
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<tr>
<td>UM</td>
<td>PM</td>
<td>0.1%</td>
<td>3</td>
</tr>
<tr>
<td>UM</td>
<td>UM</td>
<td>0.8%</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.0%</td>
<td>5030</td>
</tr>
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# RESULTS:

<table>
<thead>
<tr>
<th>Gene Analyzed</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>Allele 1: *2</td>
<td>Intermediate Metabolizer*</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Allele 1: *1</td>
<td>Normal (Extensive) Metabolizer*</td>
</tr>
<tr>
<td></td>
<td>Allele 2: *5</td>
<td></td>
</tr>
<tr>
<td>Duplication:</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Please provide Psychiatry GPS Patient Handouts 102 and 208 to patient. Handouts are also available at [www.cincinnatichildrens.org/ppainfo](http://www.cincinnatichildrens.org/ppainfo).

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**Common differences in the CYP2C19 gene can affect how you respond to medicines**

**Your CYP2C19 Genetic Test Results and What They Mean**

**CYP2C19: Intermediate Metabolizer #102**

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**Your doctor may use your test result to choose the medicine most likely to work or to choose the best dose of medicine for you. A number of medicines could be affected. The following are among those broken down by the CYP2C19 enzyme:**

- Antidepressants: citalopram, escitalopram, paroxetine, sertraline, trazodone
- Antipsychotics: clozapine, olanzapine, quetiapine, risperidone, ziprasidone
- Cimetidine
- Carbamazepine
- Nortriptyline
- Ticlopidine
- Trazodone

**The CYP2C19 enzyme activity can also be affected by some foods. It is important to tell the doctor all the medicines and supplements you are taking:**

Research continues to be done on what medications are affected by genetic test results. For more details about which medicines are broken down by CYP2C19, please go to [www.cincinnatichildrens.org](http://www.cincinnatichildrens.org) or email [pmp@chmc.org](mailto:pmp@chmc.org).

Questions about individual health concerns or specific treatment options should be discussed with your physician.
Patients are asking for genetic testing or bringing reports

Do you use PGx?
Do patients ask questions about genomics?
Do you feel comfortable talking about genomics with your patients?
Do you want additional PGx education?

Child & Adolescent Psychiatry
Adolescent Medicine
Developmental & Behavioral Pediatrics

2016 Grassroots genomics survey of providers at CCHMC.
Other specialties are starting to catch on

Time to target voriconazole concentration faster in transplant patients with genotype-guided dosing

Median time to target: 6.5 days vs 29 days
Median duration of prophylaxis: 46.5 days vs 65 days

Gene Analyzed: **CYP2D6**
Allele 1: *9
Allele 2: *5
Duplication: No

**Predicted Phenotype** – Intermediate Metabolizer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>100% standard starting dose</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>100% standard starting dose</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>100% standard starting dose</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100% standard starting dose</td>
</tr>
</tbody>
</table>

8% of patients have actionable genotypes for **CYP2D6**
Can be ordered prior to surgery, regularly done now for pectus excavatum

Alert always fires to look at results, not just actionable results
What have we learned?

• Having hospital leadership on board was instrumental
• CCHMC psychiatrists want a panel of medications because they have many options and switch frequently
• CCHMC psychiatrists like the dosing recommendations with percentage of normal dose
• Even though report is available on most psychiatry patients, it’s not always used (too many clicks to see results)
• Insurance reimburses for tests when they are ordered at an inpatient encounter
Where do we go from here?

• Improve decision support
  – Put results in as discrete data along with PDF so results are easily accessible and CDS can be driven off them
  – Alert only when actionable results are in report
• Implement additional gene-drug pairs
• Learn from the patients already tested
• Improve education for clinicians
• Continue research efforts
Ongoing research efforts

• Retrospective study to analyze response to neuropsychiatric medications and whether additional genes will improve prediction of response
• Pain pharmacogenetics & epigenetics – Vidya Chidambaran, Parinda Metha
• Transplant pharmacogenetics – cost effectiveness study of genotype-guided tacrolimus (eMERGE)
• Pharmacogenomics of response to methylphenidate in kids with ADHD
• Pharmacogenomics of response to methotrexate in kids with arthritis
A toxic tale - improved

- Genetics - found to be a CYP2D6 poor metabolizer and dosages adjusted - Side effects greatly reduced
- Drug selection altered but still with ongoing behavioral problems
- Future development of a pharmacokinetic model may improve chances for best response
changing the outcome together

Co-Directors

Clinical Pharmacists

Division of Human Genetics

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Laura.Ramsey@cchmc.org  @drlauraramsey  

Cincinnati Children’s
changing the outcome together